Polymerized human Hb use in acute chest syndrome: a case report

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BACKGROUND: Acute chest syndrome (ACS) is a complication of sickle cell disease that can cause significant morbidity. Transfusion therapy has been shown to significantly increase oxygenation in patients with ACS and RBC exchange is considered the standard of care in patients at high risk of respiratory failure.

CASE REPORT: A patient with ACS and several high-risk features, including thrombocytopenia, profound anemia, bilateral pulmonary infiltrates, staphylococcal sepsis, and pulmonary embolism is presented. The patient refused transfusion on religious grounds and received 12 units of human polymerized Hb solution (poly SFH-P injection, PolyHeme, Northfield Laboratories) over the course of 13 days. The patient's respiratory status improved and she was discharged home without receiving RBC transfusions.

CONCLUSION: This is the first reported case that describes the use of PolyHeme in a patient with sickle cell disease, ACS, and sepsis. This therapy is thought to have been lifesaving for this patient.

Acute chest syndrome (ACS) is the most common pulmonary complication and the leading cause of death in patients with sickle cell disease.[1,2] Although its pathogenesis is poorly understood, important factors related to the development of ACS are thought to include macro- and microvascular infarction, pulmonary fat embolism, infection, rib infarction, and pulmonary edema.[3] Once the process starts, an unfortunate cycle ensues with hypoxia leading to the formation of irreversibly sickled RBCs that cause further hypoxia in the tissues.[3]

The optimal therapy for ACS remains unclear; supportive care including antibiotics and transfusion therapy is commonly used. Transfusion therapy is used to decrease the percentage of HbS and correct anemia. Exchange transfusion replaces RBCs that contain HbS with cells that contain HbA. The goal of this therapy is to decrease the percentage of HbS to less than 30 percent of the total Hb. This prevents further sickling of RBCs and helps to break the cycle of continued hypoxia.

ABBREVIATIONS: ACS = acute chest syndrome; CBC = complete blood count; HBOC(s) = Hb-based oxygen carrier(s); P_{50} = the partial pressure of oxygen where Hb is 50% saturated with oxygen.

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In an analysis of 671 episodes of ACS in 538 patients treated at 30 centers by Vichinsky et al.,[2] 72 percent received RBC transfusion (68% simple transfusion). Oxygenation significantly increased with transfusion. They concluded that patients at high risk for respiratory failure including adults, patients whose presentation includes severe pain in the arms and legs, and patients who present with anemia or thrombocytopenia along with multilobar pneumonia should receive transfusion therapy.

We recently treated an adult patient with a human polymerized Hb solution (poly SFH-P injection, PolyHeme Northfield Laboratories, Evanston, IL). This patient, who refused transfusion on a religious basis, presented with a vasoocclusive crisis and developed bilateral pulmonary infiltrates, pulmonary embolism, staphylococcal bacteremia, a profound anemia, and thrombocytopenia and would have met the above criteria for early transfusion therapy.

CASE REPORT

A 26-year-old African American woman with a history of sickle cell anemia was admitted to the Johns Hopkins Hospital medical service with a 48-hour history of bilateral elbow, knee, and back pain. The patient had documented glucose-6-phosphate dehydrogenase deficiency and was a Jehovah's Witness.

On admission the patient was febrile to 39.1°C, diaphoretic, and uncomfortable. Her conjunctiva were icteric and there was an II/VI systolic ejection murmur. Lung exam was clear and she was noted to have bilateral knee effusions. Her laboratory data are listed in Table 1. The patient was treated with parenteral opioids, ketorolac, prophylactic subcutaneous heparin, gatifloxacin, supplemental oxygen, folate, and IV hydration. Three days into admission the patient's pain was well controlled, although she remained febrile. A fall in platelet count was noted, so prophylactic heparin was discontinued. That evening the patient required increasing amounts of supplemental oxygen with oxygen saturations of 88 percent on 40 percent supplemental oxygen. A chest X-ray demonstrated a new left lobe infiltrate. Antibiotic coverage was broadened to include ceftriaxone. Over the next 12 hours, the patient's oxygen demands increased; a blood gas obtained when the patient was on 60 percent nonrebreather face mask showed hypoxemia and repeat complete blood count (CBC) revealed worsening anemia (Table 1). A computed tomography scan of the chest demonstrated a left main pulmonary artery defect consistent with pulmonary embolism and bilateral consolidation. Blood cultures grew *Staphylococcus aureus.* Lower extremity Doppler ultrasound demonstrated a right midpopliteal deep venous thrombosis. The clinical findings of chest infiltrates, fever, and hypoxemia established the diagnosis of ACS. Her blood smear was notable for RBC changes consistent with both sickle cell disease and oxidant hemolysis (Fig. 1). The reticulocyte count fell (Fig. 2).

After discussion with the attending physician, the patient declined RBC transfusions and exchange transfusion that ordinarily would have been performed at our institution to prevent worsening pulmonary function. The patient's management consisted of supplemental erythropoietin therapy (40,000 units subcutaneous 1 time), iron (325 mg ferrous sulfate 3 times a day), folate, oxygen, antibiotics, intravenous fluids, and pain medicine. An inferior vena caval filter was placed on hospital day 4. As our institution was involved in clinical trials with PolyHeme, it was readily available for use in this patient. Written informed consent was obtained for the

TABLE 1. Patient's laboratory values on admission and on Day 4 of hospitalization

	Admission	Fourth hospital day
WBC (number/mm^3)	44,509	32,604
RBC count (million/mm^3)	2.56	1.77
Hb (g/dL)	7.7	5.0
Hct (%)	22.4	15.1
Mean corpuscular volume	87.5	85.3
RBC distribution width (%)	18.4	18.2
Platelet (thousand/mm^3)	362	72
Na (mEq/L)*	132	129
K (mEq/L)	4.5	4.4
Chloride (mEq/L)	96	231
CO_2 (mEq/L)	20	
Blood urea nitrogen (mg/dL) 8		
Cr (mg/dL)	0.8	
Glucose (mg/dL)	143	
Total bilirubin (mg/dL)	1.9	
pH		7.44
pCO_2 (mmHg)		35
pO_2 (mmHg)		68
FiO_2†		60% nonrebreather

* mEq = milliequivalent.
† FiO_2 = fraction of inspired oxygen.

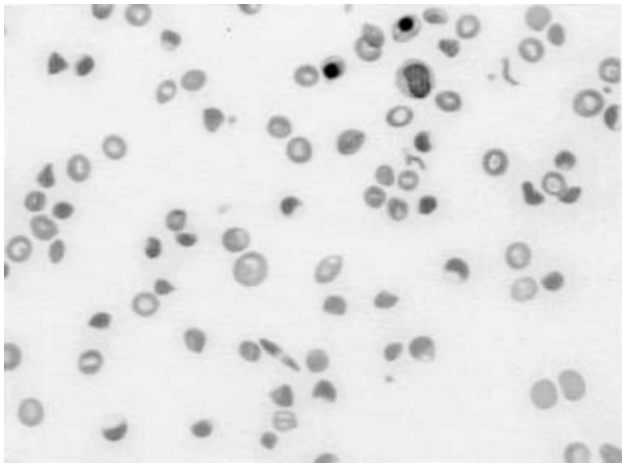
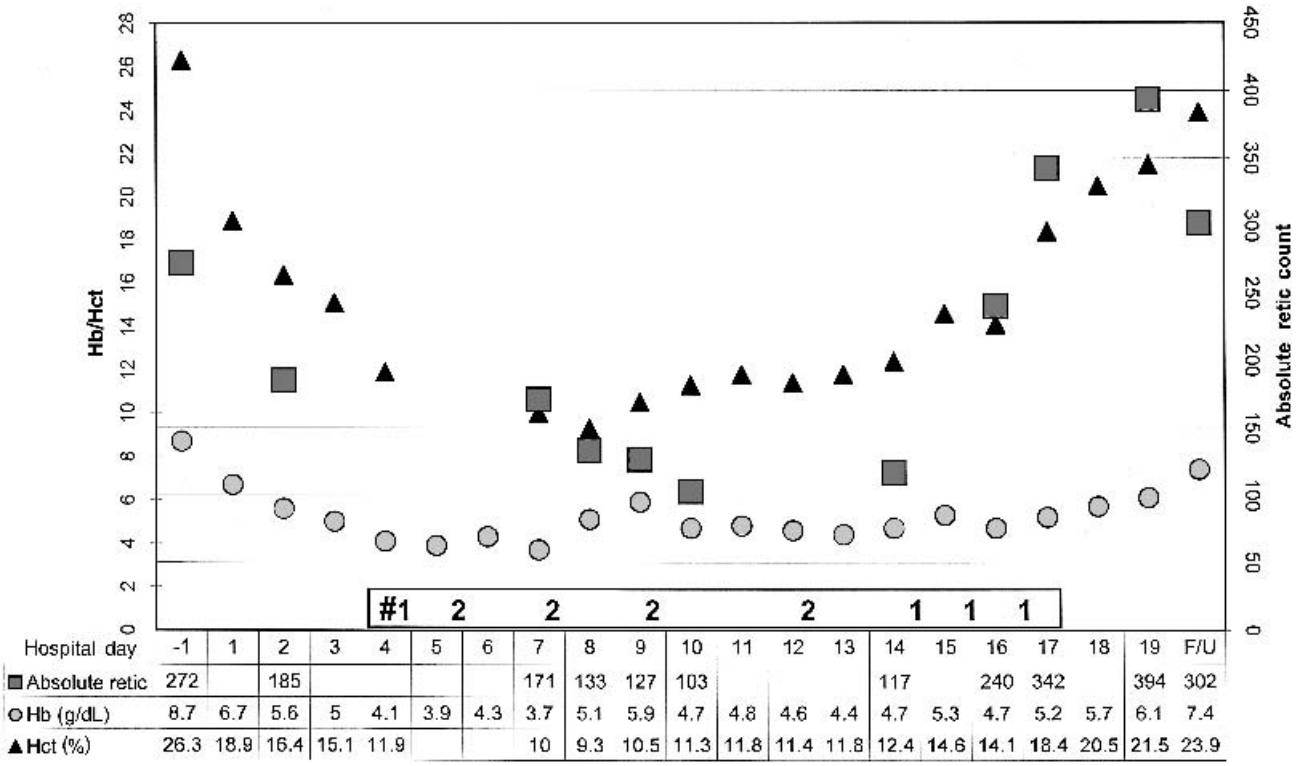


Fig. 1. Peripheral blood smear showing nucleated RBCs, sickle forms, and blister cells.



Hospital day	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	F/U
■ Absolute retic	272		185					171	133	127	103				117		240	342		394	302
○ Hb (g/dL)	8.7	6.7	5.6	5	4.1	3.9	4.3	3.7	5.1	5.9	4.7	4.8	4.6	4.4	4.7	5.3	4.7	5.2	5.7	6.1	7.4
▲ Hct (%)	26.3	18.9	16.4	15.1	11.9			10	9.3	10.5	11.3	11.8	11.4	11.8	12.4	14.6	14.1	18.4	20.5	21.5	23.9

Fig. 2. Patient's Hb, Hct, and absolute reticulocyte count during her hospitalization. (#), Units of PolyHeme were given on that hospital day; (■) absolute reticulocyte count; (●), Hb (g/dL); (▲) Hct (%). retic = reticulocyte; F/U = follow-up.

compassionate use of PolyHeme. Approval was obtained from the institutional review board and the FDA.

MATERIALS AND METHODS

PolyHeme is a pyrogen-free isotonic and isooncotic Hb solution with a Hb concentration of 10 g per dL. It contains sodium chloride, potassium chloride, and pyrogen-free water. The P_{50} is between 28 and 30 mmHg. The percentage of methionone-Hb is less than 3 percent and it contains less than 1 percent unpolymerized tetrameric Hb. The osmolality ranges from 280 to 360 m*M*.

PolyHeme was infused at a rate of 125 mL per hour; each unit contained 50 g of Hb in 500 mL. The goal was to maintain a total Hb concentration (RBC + plasma) of greater than 5.0 g per dL. Given the patient's low Hb, blood sampling was limited to essential testing. Safety was assessed by monitoring vital signs, laboratory tests (CBC and reticulocyte count), and symptoms.

RESULTS

The patient received the first dose of PolyHeme on the fourth hospital day. Over the ensuing 12 days the patient received an additional 11 units. There was no significant difference between the patient's respiratory rate, oxygen saturation, or blood pressure before or after each transfusion. There was, however, a significant difference in heart rate. The median of heart rate measurements before the start of the transfusions was 97.5 (interquartile range, 82.5-100), and immediately after the completion of the transfusions the median was 80 (interquartile range, 76-86.5; p = 0.014) (Fig. 3).

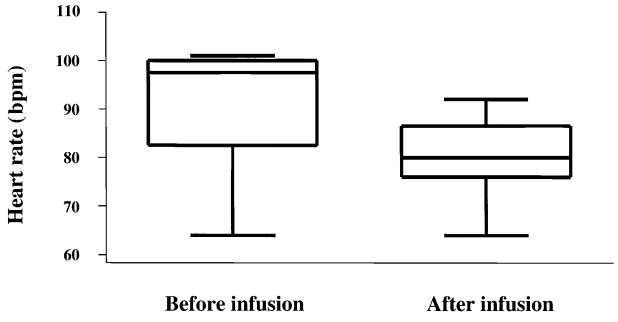


Fig. 3. The median and interquartile range of heart rate measurements before the start of the PolyHeme transfusions and immediately after the completion of the transfusions (p = 0.014). bpm = beats per minute.

The patient's respiratory status continued to be tenuous after starting PolyHeme. Weight gain, physical exam, and chest radiographs (Fig. 4) were consistent with volume overload. An echocardiogram demonstrated normal left ventricular function and the patient responded to

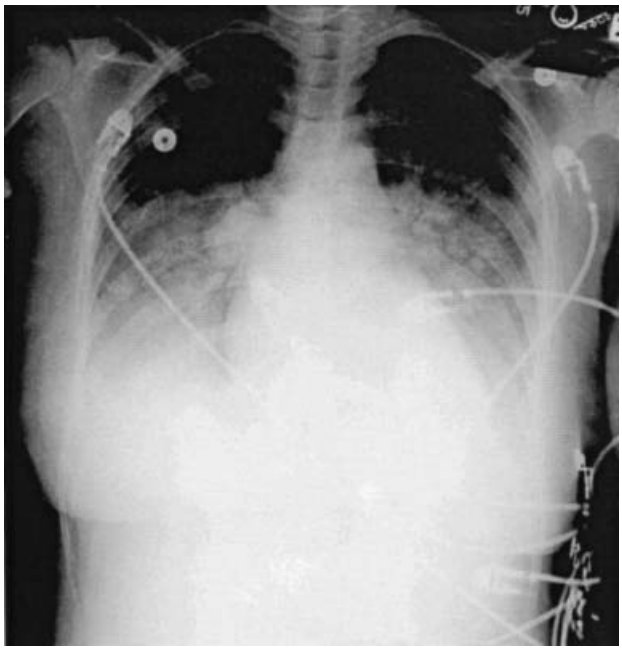


Fig. 4. Chest radiograph demonstrating bilateral effusions.

furosemide, initially requiring 120 mg. Additional units of PolyHeme were given in conjunction with 80 mg of furosemide, and volume overload was avoided. The patient slowly improved, with continued PolyHeme administration maintaining the Hb above 4.5 g per dL. Figure 2 shows the patient's Hb and reticulocyte count during her hospitalization. Hb levels immediately after transfusion were not routinely measured as blood draws were limited due to the patient's anemia. Clinical course after transfusion was uncomplicated. The patient was discharged home on hospital Day 20. A CBC performed 8 days after discharge revealed a Hb of 7.4 g per dL.

DISCUSSION

Work on the development of a safe blood substitute began 60 years ago.[4] Significant toxicity including renal dysfunction, gastrointestinal distress, and systemic vasoconstriction occurred with the initial Hb-based oxygen carriers (HBOCs). The presence of free tetrameric Hb in blood vessels was discovered to be a cause of these toxicities. The Hb tetramer binds to nitric oxide in the vessel lumen and in its free state can also extravasate through the endothelium and into the interstitial space where it binds to nitric oxide. Nitric oxide is then no longer available to act on the smooth muscle in the wall of the blood vessel and there is unopposed vasoconstriction.[4] This observation has led to the development of polymerized Hb components. These components are made by intermolecular cross-linking of tetramers. The polymer exists only in the lumen and cannot extravasate through the endothelium.

These HBOC have demonstrated the ability to enhance oxygen delivery. In a study of a bovine-derived oxygen carrier, normal male subjects were administered the bovine material or lactated Ringer's after phlebotomy and isovolemic hemodilution.[5] In this study the diffusion capacity and arterial oxygen concentration increased in the treatment group. In the control group the diffusion capacity decreased and the arterial oxygen concentration did not rise to the degree that was seen in the treatment group. The authors conclude that these changes were consistent with the more rapid diffusion of oxygen into the pulmonary capillary bed. In another study by Kasper et al.,[6] patients undergoing preoperative hemodilution for elective abdominal aortic surgery were randomly assigned to receive either bovine HBOC or 6 percent HES. In this study patients who received HBOC had better oxygen-carrying capabilities but also had increased systemic vascular resistance, which decreased the oxygen delivery index.

PolyHeme is an oxygen carrier that is derived from human Hb. The Hb to make this component is recovered from outdated blood by a process of washing and lysing the RBCs. The removal of the RBC membranes leads to the removal of RBC antigens. The PolyHeme therefore is universally compatible and has a decreased risk of causing delayed transfusion reactions. Studies that used the human-derived PolyHeme have not been associated with the vasoconstriction seen with other components, presumably because PolyHeme is a tetramer-free preparation. In a randomized trial comparing the use of PolyHeme with transfusion of allogeneic RBCs in 44 trauma patients, there were no serious or unexpected adverse events including no evidence of vasoconstriction.[7] Patients receiving PolyHeme used less allogeneic blood than those that were on the transfusion arm. In this same study by measuring arterial and venous oxygen concentrations, PolyHeme was shown to load and unload oxygen as effectively as RBCs. In a recent case report, PolyHeme was used successfully to support a Jehovah's Witness who suffered trauma and had a Hb of 3.2 g per dL.[8]

The affinity of PolyHeme for oxygen (P_{50}, 28-30) may be slightly greater than that of sickle Hb for oxygen (P_{50}, 30);[9] there is concern, therefore, that PolyHeme might steal oxygen from RBCs with sickle Hb causing these cells to sickle and induce crisis. Gonzalez et al.[10] enrolled 18 asymptomatic sickle cell patients in a placebo-controlled, dose escalation study with bovine polymerized Hb. The maximum dose given was 0.6 g per kg. The transfusions were well tolerated without evidence of toxicity. One patient developed a sickle cell crisis that was thought to be related to exercise testing. The patients who received bovine Hb were able to perform exercise testing with less of an increase in heart rate than those patients that had received saline transfusions.

In our patient the risk of respiratory failure and death, without transfusion therapy, was high. The mortality in patients with staphylococcal bacteremia is 23 percent with a pulmonary source of infection being an independent risk factor for 30-day mortality.[11] The in-hospital mortality of a patient with an acute pulmonary embolism is 22 percent.[12] The mortality of a Jehovah's Witness with ACS is unknown. In a review of patients enrolled in the cooperative study of sickle cell disease, 1722 treated episodes of ACS were examined; the mortality in adults was 4.3 percent.[1] Given this patient's high risk for mortality, the decision to proceed with compassionate use of PolyHeme was made. She tolerated the PolyHeme with minimal complications. There was no evidence of vasoconstriction as her blood pressure remained unchanged during the transfusion. The significant decrease in heart rate may be attributed to an increase in intravascular volume from the transfusion of PolyHeme, which is a volume expander. If this were the only benefit, however, one would expect that this would dilute the Hb and possibly worsen oxygen delivery. It is likely then that the decrease in heart rate reflects a decreased need for a high cardiac output because of an improvement in tissue oxygenation.

There was no significant change in respiratory rate or tissue oxygen as measured by pulse oximetry during the transfusions. The reasons for the lack of significant changes in these variables are likely multifactorial. These tests, in a single patient, may not have been sensitive enough to detect changes in tissue oxygenation. The pulse oximeter is also of questionable reliability in patients with sickle cell disease.[13] In this highly complicated patient, there were many variables including changes in fraction of inspired oxygen and issues related to pain control and volume status that affected both the respiratory rate and the overall oxygen status. These factors may have decreased the sensitivity of the respiratory rate and pulse oximetry in reflecting improved tissue oxygenation from the PolyHeme.

In our patient, there appears to have been suppression of RBC production as reflected in a decrease in reticulocyte count. This is unlikely to be from the PolyHeme as previous studies that used Hb transfusions have shown that rather than suppressing hematopoiesis, these solutions stimulate the production of RBCs as reflected by increases in reticulocyte counts during the transfusion period.[14] In a study by Hughes et al.[15] subjects who underwent phlebotomy and hemodilution followed by transfusion of bovine Hb had increases in reticulocyte counts similar to control patients who were infused with Ringer's lactate. These patients also had increases in their erythropoietin levels greater than those in control subjects. In this patient, *S. aureus* sepsis was a likely cause of marrow suppression.

Significant increases in Hb were not seen during the transfusion period, as these measurements were limited to once daily draws. Along with suppression of the reticulocyte count, the patient presumably had continued hemolysis secondary to both her acute illness and her sickle cell disease. Over a 24-hour period the benefit of the PolyHeme was not seen as the Hb fell secondary to hemolysis.

In summary we present the first reported case of a sickle cell patient with ACS who was treated with a Hb-derived oxygen carrier. PolyHeme was able to support a patient with sickle cell disease, ACS, pulmonary embolism, staphylococcal bacteremia, markedly reduced oxygen-carrying capacity due to profound anemia, and impending respiratory failure who refused transfusion of RBCs. This therapy is thought to have been lifesaving for this patient. The lack of RBC antigens in PolyHeme makes this a useful agent for patients with sickle cell disease who have alloimmunization to common RBC antigens. Future randomized studies to test the safety and efficacy of this agent, with the goal of minimizing RBC exposure for patients with sickle cell disease, may be instructive.

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